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DOI: https://doi.org/10.1093/alcalc/agq017

Alcohol & Alcoholism Vol. 45, No. 3, pp. 271–277, 2010 doi: 10.1093/alcalc/agq017
Advance Access Publication 26 March 2010

TREATMENT

Why is Disulfiram Superior to Acamprosate in the Routine Clinical Setting? A Retrospective Long-Term Study in 353 Alcohol-Dependent Patients

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(*Received* 7 *May* 2009; *accepted* 10 *March* 2010)

ABSTRACT — Aims: To compare the long-term effectiveness of acamprosate (ACP) and disulfiram (DSF) in the treatment of alcohol dependence and their effectiveness in regard to patient characteristics, within a naturalistic outpatient treatment setting. **Method:** Retrospective data from 2002 to 2007 were analysed on 353 alcohol-dependent subjects in outpatient treatment, who, according to the patient's and the clinician's mutual decision, received either supervised DSF (with thrice-weekly appointments) or ACP (once-weekly appointments) following an inpatient alcohol detoxification treatment. Abstinence was assessed by alcohol breathalyzer, patients' self-report, urine and serum analyses, and overall physicians' rating. **Results:** Baseline data in terms of current addictive behaviour and course of disease differed between groups to the disadvantage of the DSF group; compared to the ACP group, subjects treated with DSF showed a longer duration of alcohol dependence, higher amounts of daily alcohol consumption and more alcohol detoxification treatments in their history. In follow-up, Kaplan–Meier survival analysis revealed significant differences between groups in the primary and secondary measures of outcome (P always <0.01). Time elapsed before the first alcohol relapse as well as attendance to outpatient treatment and cumulative alcohol abstinence achieved within outpatient treatment was explicitly longer in the DSF group. A longer duration of alcohol dependence predicted a favourable treatment outcome in the DSF group, while for the ACP group the chances for a successful treatment increased with shorter duration of alcohol dependence. **Conclusions:** This study supports the thesis that supervised DSF is an important component of alcoholism treatment, and it appears to be more effective than the treatment with ACP particularly in patients with a long duration of alcohol dependence.

INTRODUCTION

Pharmacological relapse prevention has been shown to improve the results of psychosocial treatment of alcohol dependence (Berglund *et al.*, 2003; Bouza *et al.*, 2004; Chick *et al.*, 2003; Garbutt *et al.*, 2005; Kranzler and Van Kirk, 2001).

A large number of substances have been investigated in the field of alcohol relapse prevention. The NMDA receptor modulator acamprosate (ACP), the μ-opioid antagonist naltrexone (NTX) and the acetaldehyde dehydrogenase inhibitor disulfiram (DSF) are the best evaluated and established pharmacological options (Mann, 2004). Pooled analyses on ACP (Kranzler and Gage, 2008; Lesch *et al.*, 2001; Mann *et al.*, 2004; Verheul *et al.*, 2005) and on DSF (Berglund *et al.*, 2003) and controlled trials of supervised DSF (Brewer, 1993; Chick *et al.*, 1992; Petrakis *et al.*, 2007) have confirmed the efficacy of these treatments in the maintenance of alcohol abstinence. Few controlled studies have directly compared the effectiveness of the deterrent DSF to the so-called anticraving substances ACP or NTX.

The first published randomized controlled trial comparing supervised NTX with supervised DSF in alcoholism showed that DSF was significantly more effective, even though NTX patients reported lower craving levels (de Sousa and de Sousa, 2004). The same authors carried out a similar, 'open' study comparing DSF and ACP, obtaining very similar results in favour of DSF (de Sousa and de Sousa, 2005). Supervised treatment with DSF was also superior to both NTX and ACA in a study published by Laaksonen *et al.* (2008).

However, there may be limits to the transferability of these research studies from varying cultures to a different clinical routine. Setting, proceeding and duration of the treatment as well as selection of patients in randomized, controlled clinical trials may differ from clinical practice, and treatment approaches and options also differ between countries, even within Europe (Soyka and Chick, 2003). For instance, ACP and DSF are approved in Germany, whereas NTX is currently not licensed for relapse prevention in alcoholism.

The objective of this study was to compare retrospectively the long-term effectiveness of acamprosate (ACP) and disulfiram (DSF) in the treatment of alcohol dependence, with attention to differences in patient characteristics, within a naturalistic outpatient treatment setting in Germany.

METHODS

Setting

This study represents our routine clinical practice that corresponds to typical procedures in Germany as well as in several other countries in Europe. Our university hospital draws from an urban and suburban area in the southwest of Germany. The treatment unit for alcohol disorders accepts all alcohol-dependent patients living in the vicinity. The standardized therapy combines a 3-week inpatient treatment with a following outpatient treatment. The inpatient treatment programme (called 'Qualified Alcohol Detox') consists of alcohol detoxification, elements of a psychosocial treatment and, in consenting patients, initiation of pharmacological relapse prevention. In Germany, DSF broadly has the reputation of being dangerous and antiquated and in routine practice is used not as first choice but only after other treatments have failed, whereas ACP tends to be the pharmacotherapy of first choice.

Our retrospective analysis refers to routine outpatient treatment within the period from July 2002 to June 2007. We examined all subjects who received DSF or ACP following an inpatient alcohol detoxification treatment. Patients received DSF or ACP according to our routine practice, by mutual agreement between clinician and patient, without any specified method of matching types of patient to a specific treatment. DSF and ACP were initiated during the last week of the 3-week inpatient treatment once written informed consent had been given. Inpatient treatment was followed by the outpatient treatment programme (Mann and Batra, 1993) with brief treatment sessions for 12 months, which can be expanded if needed. Planned outpatient contacts were a mandatory, binding agreement for all patients (DSF: every second working day, each session lasting about 10 min; ACP: once a week, each session about 20 min). High-frequency outpatient contacts in the DSF group were offered because DSF generally has no specific effect unless it is monitored and supervised by professionals or family members (Anton, 2001; Brewer, 1992; Chick, 1998; Fuller and Gordis, 2004; Hughes and Cook, 1997). As intended, the frequency of attendance turned out to be considerably higher in the DSF group

DSF was administered in a mean dose of 2.1 g per week (divided evenly across the contacts) and ACP was prescribed as 2 g per day; consumption was not supervised. Supervised DSF treatment and the follow-up sessions for ACP patients were provided by physicians experienced in addiction medicine.

Standardized data acquisition included sociodemographic data, addictive behaviour and medical history as well as laboratory data. Our routine clinical assessment of patients' addictive behaviour was performed by means of a structured interview with proven reliability and validity (Mann *et al.*, 1995). Data were generated at the beginning and at the end of the 3-week inpatient treatment as well as within the course of the outpatient treatment programme. Abstinence was assessed at every contact by alcohol breathalyzer, physicians' ratings and patients' self-reports. Significant others were also involved and asked to report any drinking of the patients. Additionally, we randomly performed urine and serum analyses at least once per month.

Subjects

Of 1180 alcohol-dependent patients consecutively admitted to inpatient detoxification treatment (within the examined 5 years), 503 subjects (43%) received pharmacologic relapse prevention (DSF or ACP), 566 (48%) rejected any kind of pharmacologic relapse prevention and 111 (9%) were not offered pharmacotherapy due to contraindications. Of the 503 subjects who received pharmacologic relapse prevention, 119 received DSF (24%) and 384 received ACP (76%). All subjects who received pharmacologic relapse prevention met DSM-IV and ICD-10 criteria for alcohol dependence, completed the 3-week inpatient treatment programme and stayed abstinent during the inpatient programme. We excluded from the following analysis 140 subjects who were not willing to participate in outpatient aftercare (DSF $N = 11$, ACP $N = 139$), resulting in a final study sample of 353 subjects (DSF $N = 108$, 31%; ACP $N = 245$, 69%). Within DSF treatment as well as within ACP treatment, characteristics of addictive behaviour and course of disease did not differ significantly between subjects that participated in the follow-up and those who did not.

Outcome measures

The outcome measures refer to the outpatient treatment programme. The primary outcome measure was time to first relapse. 'Relapse' was defined as any alcohol consumption. Blood, urine or breath samples tested positive for alcohol as well as self-reports of alcohol use were classified as relapse. We deliberately did not attempt to distinguish between 'mini-lapses', 'lapses' and 'relapses' since their verification is often inadequate in an outpatient setting. Secondary outcome measures were attendance at the outpatient treatment, accumulated time of abstinence, and safety and tolerability of the treatment.

Statistical analysis

Statistical procedures included descriptive statistics for the entire study sample as well as for the two groups (DSF vs ACP) separately. To compare the groups with respect to sociodemographic characteristics, medical history and current addictive behaviour, we performed *t* tests for the continuous variables with an approximate normal distribution and χ^2 tests for the categorical variables.

Survival analysis with Kaplan–Meier estimators and log-rank tests were used to compare the treatment groups with regard to variables indicating a duration in time. Several endpoints measure the duration of time until a specified event occurs (time until first relapse, attendance to outpatient treatment). An observation was not included in the analysis if the event of interest had not occurred by the end of the follow-up. To analyse the association between these time variables and covariates, a Cox regression was calculated. All statistical tests were two-tailed; the significance level was set at $\alpha = 0.05$. The data analysis was performed by using the systems SPSS 15.0 and SAS 9.1.

RESULTS

Baseline characteristics of the total study group

The mean duration of alcohol dependence was 13.51 years (SD 8.71, range 1–40), the mean severity of alcohol dependence in terms of the number of ICD-10 criteria met (0–6) was 4.58 (SD 0.98, range 3–6) and the mean amount of alcohol consumption prior to inpatient treatment was 253.76 g alcohol per day (SD 153.25, range 40–1000). In summary, these characteristics indicate a clinical study sample with a severe degree and a long history of alcohol dependence. The presence of one or more somatic or psychiatric diseases in addition to alcohol dependence was found in 76.2% (psychiatric comorbidity, 38.2%; non-psychiatric comorbidity, 38%), which points to the clinical burden of the study sample. Patients with psychiatric comorbidity mostly suffered from depression, anxiety disorders and additional substance abuse, not including smoking, which was reported by 76% of subjects. The severity of addiction, sequelae of addiction and psychiatric comorbidity in our sample is comparable to or even higher than findings in other clinical studies in the alcoholism field (e.g. Project MATCH Research Group, 1998; Anton *et al.*, 2006).

Table 1. Baseline differences between the disulfiram group (DSF) and the acamprosate group (ACP)

Baseline variables		Acamprosate (n = 245)		Disulfiram (n = 108)				
		M /*N*	SD /%	*M* /*N*	SD /%	χ^2	*df*	*P*
Sociodemographic data								
Age at baseline (years)	*M*, SD, *t*	48.10	10.77	42.67	8.64	5.03	251.84	<0.01**
Female patients	*N*, %, χ^2	90	36.7	21	19.4	10.40	1	<0.01**
No school-leaving qualification	*N*, %, χ^2	9	3.7	5	4.6	4.70	1	0.20
No vocational education	*N*, %, χ^2	41	16.7	41	37.9	16.45	1	<0.01**
Registered unemployed	*N*, %, χ^2	99	40.41	69	63.9	22.91	1	<0.01**
Not living in partnership	*N*, %, χ^2	140	57.14	56	51.85	0.97	1	0.32
Characteristics and history of the addiction								
Duration alcohol dependence (years)	*M*, SD, *t*	12.27	8.41	16.53	8.73	3.87	155.19	<0.01**
Severity of alcohol dependence (ICD-10 criteria)	*M*, SD, *t*	4.17	0.96	4.36	1.02	−0.50	24	0.6245
Alcohol consumption before admission (g/day)	*M*, SD, *t*	224.37	126.49	321.67	187.28	−4.50	125.50	<0.01**
Alcohol consumption before admission/weight (g/kg/day)	*M*, SD, *t*	3.03	1.72	4.41	2.50	−4.51	125.50	<0.01**
Previous max. duration of continuous abstinence (months)	*M*, SD, *t*	19.59	37.89	23.38	53.82	0.54	103.32	0.59
Previous inpatient alcohol detoxifications (number)	*M*, SD, *t*	2.31	5.44	7.76	9.63	−5.50	138.03	<0.01**
Previous inpatient withdrawal treatments (number)	*M*, SD, *t*	0.50	0.88	1.25	1.19	−5.89	160.68	<0.01**
Previous pharmacotherapeutic relapse prevention	*N*, %, χ^2	6	2.5	102	94.4	15.79	1	<0.01**
Current clinical data								
Psychiatric medication	*N*, %, χ^2	91	37.1	46	42.6	0.94	1	0.33
Non-psychiatric medication	*N*, %, χ^2	118	48.2	38	35.2	5.12	1	0.02*
Psychiatric comorbidity (axis I)	*N*, %, χ^2	92	37.6	43	39.8	0.16	1	0.69
Addiction other than alcohol dependence	*N*, %, χ^2	24	9.8	22	20.4	7.40	1	<0.01**
Somatic comorbidity	*N*, %, χ^2	121	49.4	30	27.8	14.30	1	<0.01**
Alcohol-induced somatic sequelae	*N*, %, χ^2	54	22.0	28	25.9	0.63	1	0.43
Gamma-glutamyltransferase (U/L)	*M*, SD, *t*	233.84	412.90	259.43	370.00	−0.45	133.20	0.65
Aspartate aminotransferase (U/L)	*M*, SD, *t*	67.01	72.35	90.23	92.26	−1.80	99.40	0.07
Alanine aminotransaminase (U/L)	*M*, SD, *t*	52.78	47.75	72.55	88.74	−1.70	80.00	0.09

M, mean; SD, standard deviation.
Registered unemployed: without housewives/housemen, pensioner and students.
Severity of alcohol dependence: number of fulfilled ICD-10 criteria (range 0–6).
Alcohol consumption/weight: gram alcohol/kilogram body weight.
Current clinical data: at admission to inpatient detoxification.

Baseline differences between DSF and ACP group

Sociodemographic characteristics and the medical history showed several significant differences between the two treatment groups (Table 1). These findings were not surprising since the allocation to the treatment groups was determined by a clinical decision, not by a matching procedure. Compared to the ACP group, the DSF group was about 5 years younger and the gender imbalance was more pronounced. The level of vocational education acquired was lower and the rate of registered unemployment was higher in the DSF group than in the ACP group, which is associated with poorer socioeconomic conditions of the DSF group. Likewise, course and characteristic of alcohol dependence differed between groups to the disadvantage of the DSF group. Compared to the ACP group, subjects treated with DSF showed a longer duration of alcohol dependence (in spite of the younger mean age), higher amounts of daily alcohol consumption and more alcohol detoxification treatments in their history (Table 1). Almost all patients of the DSF group formerly received acamprosate (80.4%) or naltrexone (14.3%), whereas nearly all patients treated with ACP received pharmacotherapeutic relapse prevention for the first time. The overall prevalence of psychiatric comorbidity did not differ significantly between both groups (DSF: 39.8% vs ACP: 37.6%), but an additional substance use disorder was found twice as often in the DSF group (20.4%) than in the ACP group (9.8%).

The prevalence of somatic comorbidity revealed differences to the disadvantage of the ACP group regarding internal ailments only. However, alcohol-induced internal diseases (liver steatosis, cirrhosis, hepatitis, pancreatitis) as well as elevation of the alcohol-related laboratory values alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase did not show significant differences between groups. As expected from the imbalance of the prevalence of

Table 2. Outcome differences between the disulfiram group (DSF) and the acamprosate group (ACP)

Outcome variables	Acamprosate			Disulfiram				
	N	Median	CI	*N*	Median	CI	χ^2	*P*
Attendance to treatment (months)	245	2.66	2.00–3.60	108	14.90	14.00–19.00	54.42	<0.01**
Time until first relapse (months)	112	1.00	0.50–1.00	66	3.50	2.00–4.50	18.44	<0.01**
Cumulated time of abstinence (months)	245	2.00	1.50–2.40	108	9.75	5.50–12.50	51.49	<0.01**

CI, confidence interval.
Relapse: any alcohol consumption.

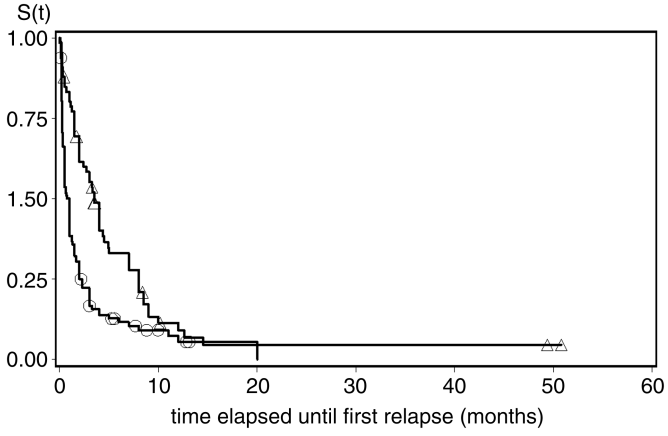

Fig. 1. Time elapsed until first relapse in the disulfiram group (open triangles) and the acamprosate group (open circles). Kaplan–Meier survival curves showing time (number of months) to first relapse in the outpatient treatment. S(t): survival as a function of time, *P*-values; open triangles: censored observation, disulfiram group (DSF); open circles: censored observation, acamprosate group (ACP). Cases were censored if they have not experienced an event.

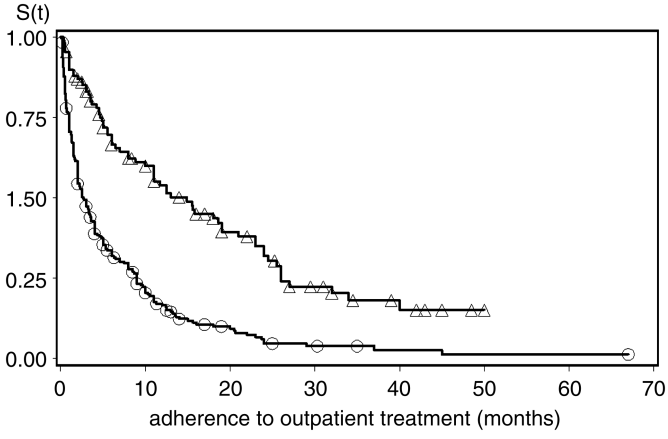

Fig. 2. Attendance to outpatient treatment in the disulfiram group (open triangles) and the acamprosate group (open squares). Kaplan–Meier survival curves showing adherence to outpatient treatment (number of months). S(t): survival as a function of time, *P*-values; open triangles: censored observation, disulfiram group (DSF); open circles: censored observation, acamprosate group (ACP). Cases were censored if they have not experienced an event.

somatic comorbidity, the ACP group received significantly more non-psychiatric pharmacotherapy, whereas the frequency of psychopharmacotherapeutic co-medication did not differ between both groups (DSF: 42.6% vs ACP: 37.1%).

Treatment outcome DSF versus ACP

The Kaplan–Meier survival analysis revealed highly significant differences between groups in the primary and secondary measures of outcome (P always <0.01, Table 2 and Figs 1–3). Time elapsed before the first alcohol relapse was significantly longer in the DSF group [median 3.50 months, 95% confidence interval (CI) 2.00–4.50] compared to the ACP group (median 1.00 months, 95% CI 0.50–1.00). Likewise, attendance at outpatient treatment was significantly longer in the DSF group (median 14.90 months, 95% CI 14.00–19.00) than in the ACP group (median 2.66 months, 95% CI 2.00–3.60). Consistent with these results, the cumulative alcohol abstinence achieved within outpatient treatment was longer in the DSF group (median 9.75 months, 95% CI 5.50–12.50) than in the ACP group (median 2.00 months, 95% CI 1.50–2.40). In accordance with these results, all alcohol-related laboratory values decreased significantly (on average about 50% within the first month) without significant differences between the DSF group and the ACP group.

Predictors of outcome DSF versus ACP

In order to determine whether treatment-group-related differences in the patients' baseline characteristics predict treatment outcome, we separately performed a Cox regression analysis in continuous independent variables and a log-rank test in categorical independent variables for both treatment groups.

Of the variables regarding medical history and sociodemographic characteristics, only a small number predicted the measures of outcome. In the DSF group, the variable 'gender' and the variable 'duration of alcohol dependence' showed a significant prognostic impact. Female gender predicted a significant longer attendance to the treatment compared to male gender ($P = 0.03$, $T = 4.48$) in the DSF group. In this treatment group, exclusively the variable 'duration of alcohol dependence' significantly predicted both the primary and secondary outcome measures, irrespective of gender. 'Duration of alcohol dependence' correlated positively with time to first

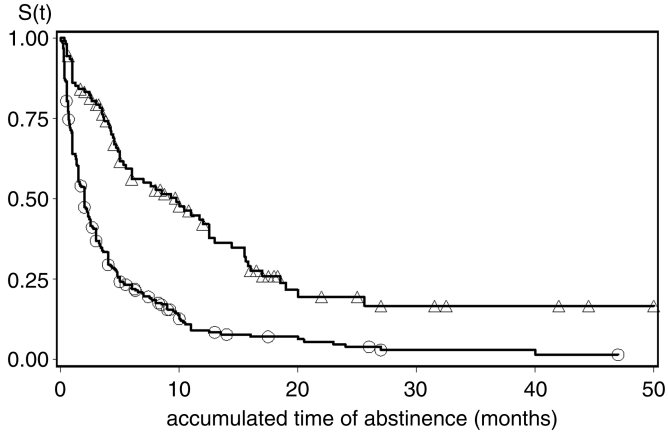

Fig. 3. Accumulated time of alcohol abstinence in the disulfiram group (open triangles) and the acamprosate group (open circles). Kaplan–Meier survival curves showing accumulated time of alcohol abstinence (number of months) within outpatient treatment. S(t): survival as a function of time, *P*-values; open triangles: censored observation, disulfiram group (DSF); open circles: censored observation, acamprosate group (ACP). Cases were censored if they have not experienced an event.

relapse ($P = 0.03$, $T = 4.77$) and with attendance at treatment ($P = 0.01$, $T = 5.93$).

In the ACP group, the variables 'age' and 'vocational education' and the variable 'duration of alcohol dependence' showed a significant prognostic impact. 'Age' correlated negatively with attendance at the treatment ($P = 0.01$, $T = 6.49$). 'Vocational education' correlated negatively with time elapsed previous to the first relapse ($P = 0.00$, $T = 23.28$). Thus, younger age and lower vocational education were associated to a better outcome. Again, in the ACP group, the variable 'duration of alcohol dependence' exclusively showed a significant impact on both primary and secondary measures of outcome. However, in contrast to the DSF group, the duration of alcohol dependence correlated negatively with the time to first relapse ($P = 0.02$, $T = 5.78$) as well as attendance to the treatment ($P = 0.00$, $T = 8.11$). In the ACP group, a shorter duration of alcohol dependence predicted a longer time to first relapse and a longer attendance at treatment.

Safety and tolerability

We found significantly more adverse events in the DSF group (62%) compared to the ACP group (48%, $P = 0.02$). Tiredness during the day in combination with sleep disturbances was the most prominent adverse event by far in the DSF group (DSF: 50% vs ACP: 15.9%, $P < 0.01$). Gastrointestinal complaints were the most prominent adverse event in the ACP group (ACP: 31.8% vs DSF: 14.8%, $P < 0.01$). None of the adverse events was life threatening. Despite finding significantly more adverse events in the DSF group than the ACP group, drop-out rates due to adverse events did not differ between groups and were low (<5%).

Treatment costs DSF versus ACP

Using the mean cost at our site for comparison, the lower price for DSF pharmacotherapy (21€/month) compared to ACP (130€/month) was accompanied by higher costs for supervised DSF treatment with high-frequency contact to professionals (275€/month) compared to ACP (145€/month), the total cost per patient per month being estimated as: DSF 296; ACP 275 (1€ = US$ 1.36, 0.91 GBP).

DISCUSSION

This retrospective study of pharmacotherapeutic relapse prevention within routine treatment of alcohol dependence suggests that supervised treatment with DSF is more effective than treatment (unsupervised) with ACP, a conclusion supported by the fact that subjects receiving treatment with DSF tended to have had at baseline a longer duration of alcohol dependence, higher amounts of daily alcohol consumption and more previous detoxification treatments than the ACP patients. These baseline differences are not surprising since in Germany as well as in several other countries, DSF is usually not a first choice treatment, which results in a selection of patients with a longer and more unfavourable course of disease. Nevertheless, patients receiving supervised DSF treatment benefited and in fact showed better outcomes than subjects given ACP treatment. More precisely, subjects from the DSF group show longer time to the first alcohol relapse and a higher cumulative alcohol abstinence achieved within outpatient treatment. Furthermore, the rate of participation in the outpatient treatment programme is higher in patients assigned to DSF compared to patients assigned to ACP. Our evaluation in routine care adds to the results of several randomized trials (Carroll *et al.*, 1993; de Sousa and de Sousa, 2004, 2005; Laaksonen *et al.*, 2008), which found that supervised DSF tends to be more effective than ACP or NTX.

It seems probable that these results are due not only to the pharmacotherapy *per se* but also because of the close monitoring and high-frequency contact between patient and professional, which is necessary for successful treatment with DSF. Indeed, we are not only testing the effect of these pharmacological substances but also differences between the treatment package in which DSF and ACP are usually embedded. The non-pharmacological, psychological parts of these packages differ significantly between DSF and ACP (Ehrenreich and Krampe, 2004). The high-frequency contact with professionals in the supervised DSF concept persists despite more adverse drug reactions in the DSF group. Krampe *et al.* (2006) reason that a supervised long-term DSF treatment implies a psychological rather than a pharmacological action of DSF.

One may argue that the methodological limitations inherent in retrospective, non-randomized, single-site clinical studies limit the comparability of our data to results of controlled clinical trials. However, these types of treatment correspond to clinical practice that is common at our facility as well as in many facilities in Europe.

Besides the presented differences between the DSF and the ACP treatment groups, there may be other differences that we have not measured between the treatment groups as well as between the subjects that participated in the follow-up and those who did not. Although we cannot claim exclusion of confounding variables (in particular we do not have a baseline measure of patients' commitment to abstinence, a factor which might have led more committed patients to request disulfiram), we believe our results may be more practically relevant as well as generalizable than those from purer clinical studies.

Referring to the predictors of outcome, the association between better outcome and younger age and lower vocational education might be due to a willingness to accept the treatment setting. However, these sociodemographic predictors are inconsistent and should not be over-interpreted. From among the medical history and sociodemographic variables that we examined, only the variable 'duration of alcohol dependence' significantly predicted both the primary and secondary outcome measures.

Concordant with our own earlier results (Diehl *et al.*, 2007; Mann *et al.*, 2005), longer duration of alcohol dependence predicted a favourable treatment outcome in the DSF group. In contrast, in the ACP group a shorter duration of alcohol dependence predicted a better outcome. If this opposed association is not only a result of selection effects, predictive impact of the duration of alcohol dependence might enable an allocation to the most promising treatment. An undertaking to attend supervised DSF treatment is probably more readily accepted by patients with a longer duration of alcohol dependence.

CONCLUSION

This study adds to the evidence that supervised DSF is an important item in the menu of alcoholism treatments, is accepted by many patients and may be more effective than a treatment with ACP. Supervised DSF treatment might be particularly appropriate in patients with a long duration of alcohol dependence.

This evidence is contrary to the current underuse of DSF. US substance abuse specialist physicians prescribed DSF to ~9% of the alcoholic patients in the study of Mark *et al.* (2003) and German substance abuse specialist physicians probably utilize it even less (Diehl and Mann, 2007; Mutschler *et al.*, 2008). The fear of DSF hepatotoxicity and other side effects is commonly exaggerated. Death from DSF alcohol reaction also seems to be extremely rare (Chick, 1999, 2004).

In our opinion, there is no reason to keep supervised DSF treatment from suitable patients. Therefore, the notion that supervised DSF is a 'last choice treatment' should be reconsidered.

Acknowledgements — The authors would like to thank Tabea Kühl and Stefan Funke for their help in preparing the manuscript.

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